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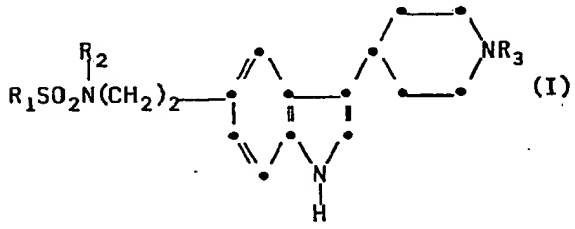
The title of the invention has been amended (Guidelines for Examination in the EPO, A-III, 7.3).

(54) 3-(4-Piperidine)-5-(2-sulfonylaminoethyl) indole derivatives.

(57) Compounds are disclosed of formula (I)



(I)

wherein
R_1 represents C_{1-6} alkyl;
R_2 represents H or C_{1-6} alkyl;
R_3 represents H or C_{1-3} alkyl;
and pharmaceutically acceptable salts and solvates (for example hydrates) thereof.

The compounds are indicated as useful for the treatment of migraine, cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders.

Processes and intermediates for their preparation and pharmaceutical compositions containing them are also disclosed.

EP 0 354 777 A2

Description

CHEMICAL COMPOUNDS

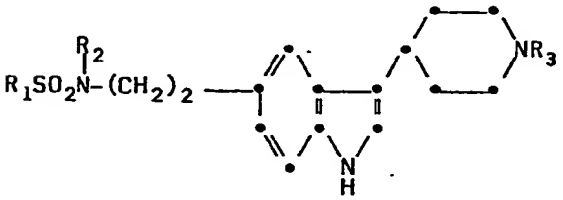
This invention relates to indole derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use, in particular to compounds and compositions of use in the treatment of migraine.

It has been suggested that the pain of migraine may be associated with excessive dilatation of the cranial vasculature and known treatments for migraine include the administration of compounds having vasoconstrictor properties such as ergotamine. However, ergotamine is a non-selective vasoconstrictor which constricts blood vessels throughout the body and has undesirable and potentially dangerous side effects. Migraine may also be treated by administering an analgesic usually in combination with an antiemetic but such treatments are of limited value.

More recently, indole derivatives which are selective $5HT_1$-like receptor agonists and which exhibit selective vasoconstrictor activity have been described in the art as useful in the treatment of migraine.

We have now found a novel group of indole derivatives which not only exhibit $5HT_1$-like receptor agonist activity and selective vasoconstriction but also unexpectedly have an enhanced overall bioavailability index following administration, in particular following non-parenteral administration.

Thus, the present invention provides an indole of formula (I):



(I)

R_1 represents a C_{1-6} alkyl group;
R_2 represents a hydrogen atom or a C_{1-6}alkyl group;
R_3 represents a hydrogen atom or a C_{1-3} alkyl group;
and pharmaceutically acceptable salts or solvates (e.g. hydrates) thereof.

As used herein a C_{1-6}alkyl group may be a straight chain or a branched chain alkyl group, preferably a C_{1-3}alkyl group such as methyl or ethyl.

In the compounds of formula (I), R_1 preferably represents a C_{1-3} alkyl group such as methyl.

R_2 in the compounds of formula (I) preferably represents a hydrogen atom.

R_3 in the compounds of formula (I) preferably represents a C_{1-3} alkyl group such as methyl.

A preferred compound according to the invention is :
N-[2-[3-(1-Methyl-4-piperidinyl)-1H-indol-5-yl]ethyl]methanesulphonamide
and its pharmaceutically acceptable salts and solvates.

Suitable pharmaceutically acceptable salts are those conventionally known in the art. Examples of pharmaceutically acceptable salts include acid addition salts formed with inorganic acids, such as hydrochlorides, hydrobromides, phosphates and sulphates, and with organic acids, for example tartrates, maleates, fumarates, succinates and sulphonates. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds of formula (I) and these form a further part of the invention.

The invention embraces all optical isomers of the compounds of formula (I) and their mixtures, including racemic mixtures thereof.

Compounds of the invention may readily be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent. It is intended to include such solvates within the scope of the present invention.

The selective $5HT_1$-like receptor agonist activity and selective vasoconstrictor activity of the compounds of the invention have been demonstrated in vitro. In addition, compounds of the invention selectively constrict the carotid arterial bed of the anaesthetised dog whilst having negligible effect on blood pressure.

Following non-parenteral, including intra-duodenal administration, the compounds of the invention show an enhanced bioavailability index in animals.

Compounds of the invention are useful in treating conditions associated with cephalic pain. In particular the compounds are useful in the treatment of migraine, cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders and in alleviating the symptoms associated therewith.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt or solvate (e.g. hydrate) thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in conventional manner using one or more pharmaceutically acceptable carriers or excipients.

In a further aspect there is provided a compound of formula (I) or a salt or solvate thereof for use in therapy,

in particular in human medicine. It will be appreciated that use in therapy embraces but is not necessarily limited to use of a compound of formula (I) or a salt or solvate thereof as an active therapeutic substance.

There is also provided as a further aspect of the invention the use of a compound of formula (I) in the preparation of a medicament for use in the treatment of conditions associated with cephalic pain in particular migraine, cluster headache, chronic paroxysmal hemicrania and headache associated with vascular disorders.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, comprising administration of an effective amount of a compound of formula (I) or salt or solvate thereof in particular in the treatment of conditions associated with cephalic pain and in alleviating the symptoms associated therewith.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds according to the invention may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

The active ingredient may conveniently be presented in unit dose form. A convenient unit dose formulation contains the active ingredient compound in an amount of from 0.1mg to 200mg.

The compounds according to the invention may for example be formulated for oral, sub-lingual, buccal, parenteral, rectal or intranasal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters or ethyl alcohol); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid).

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by injection, conveniently intravenous or subcutaneous injection, for example by bolus injection or continuous intravenous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative.

The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glyceride.

Tablets for sub-lingual administration may be formulated in a similar manner to those for oral administration.

For intranasal administration the compounds of the invention may be used, for example, as a liquid spray or powder or in the form of drops.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

It will be appreciated that the precise dose administered will depend on the age and condition of the patient, the particular compound used and the frequency and route of administration. The compound may be administered in single or divided doses and may be administered one or more times, for example 1 to 4 times per day.

A proposed dose of the compounds of the invention for oral, sublingual, parenteral, buccal, rectal or intranasal administration to man (of approximately 70kg bodyweight) for the treatment of migraine is 0.1 to 200mg of the active ingredient per unit dose which could be administered, for example, 1 to 4 times per day.

For oral administration a unit dose will preferably contain from 10 to 200 mg of the active ingredient. A unit dose for parenteral administration will preferably contain 0.2 to 15 mg of the active ingredient.

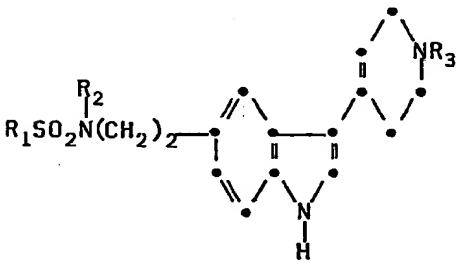
Aerosol formulations are preferably arranged so that each metered dose or 'puff' delivered from a pressurised aerosol contains 0.2 mg to 2 mg of a compound of the invention, and capsules and cartridges delivered from an insufflator or an inhaler, contain 0.2 mg to 20 mg of a compound of the invention. The overall daily dose by inhalation with an aerosol will be within the range 1 mg to 200 mg. Administration may be several times daily, for example from 2 to 8 times, giving for example 1, 2 or 3 doses each time.

Dosages of the compounds of the invention for rectal, sub-lingual or intranasal administration are similar to those for oral administration.

The compounds of the invention may, if desired, be administered in combination with one or more other therapeutic agents, such as analgesics, anti-inflammatory agents and anti-nauseants, and formulated for administration by any convenient route in conventional manner. Appropriate doses will be readily appreciated by those skilled in the art.

According to another aspect of the invention, compounds of formula (I) and pharmaceutically acceptable salts and solvates (e .g. hydrates) thereof, may be prepared by methods known in the art for the preparation of analogous compounds such as the general methods outlined below. In the following processes, R_1, R_2 and R_3 are as defined for formula (I) unless otherwise specified.

According to one general process (A) compounds of formula (I) may be prepared by reduction of the corresponding compounds of formula (II).

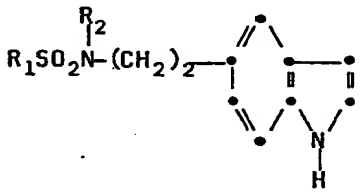


(II)

The compounds of formula (II) are themselves novel compounds and form a further part of the invention. The compounds of formula (II) have also been found to be selective $5HT_1$-like receptor agonists and potent and selective vasoconstrictors.

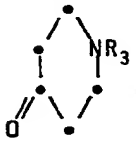
The reduction process may conveniently be carried out in the presence of hydrogen and a metal catalyst, such as palladium, Raney nickel, platinum, platinum oxide or rhodium which may be supported, for example, on charcoal. Alternatively a homogenous catalyst such as tris(triphenylphosphine) rhodium chloride may be used. The reduction may be carried out in a solvent such as an alcohol e.g. methanol or ethanol, an ether e.g. dioxan, an ester e.g. ethyl acetate or an amide e.g. dimethylformamide and conveniently at a temperature of from -10 to +50°C.

The compounds of formula (II) may be prepared by condensing a compound of formula (III):



(III)

or a protected or activated derivative thereof, with a piperidone of formula (IV):



(IV)

or a salt or protected derivative thereof.

The condensation reaction may be effected in a suitable reaction medium in the presence of an acid or a base, conveniently at a temperature of 25 to 120°C.

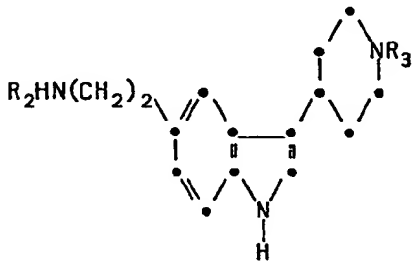
Acids which may be employed in the above process include organic and inorganic acids such as sulphonic acids (e.g. p-toluenesulphonic acid), carboxylic acids (e.g. acetic acid) and preferably strong inorganic acids such as polyphosphoric acid, sulphuric acid and hydrochloric acid. Suitable solvents for the reaction include inert solvents such as ethers (e.g. tetrahydrofuran or dioxan), alcohols (e.g. ethanol) and chlorinated hydrocarbons (e.g. chloroform or carbon tetrachloride). In some cases the acid may also act as the reaction solvent.

Bases which may be employed in the above process include alkali metal hydroxides (eg. potassium hydroxide), alkali metal alkoxides (e.g. sodium or potassium methoxide, ethoxide or t- butoxide), alkali metal

hydrides (e.g. sodium hydride) and alkali metal amides (e.g. sodamide). Suitable solvents for the reaction include alcohols (e.g. methanol or ethanol), ethers (e.g. tetrahydrofuran or dioxan) and dimethylsulphoxide.

Intermediates of formula (III) may be prepared by conventional methods for example by reacting the corresponding compounds of formula (III) in which the R_1SO_2-group is replaced with a hydrogen atom with an appropriate sulphonylating agent according to the procedure described in process (B) hereinafter.

According to another general process (B), a compound of formula (I) may be prepared by reacting a compound of formula (V):



(V)

or a salt thereof (for example, an organic or inorganic acid addition salt such as the hydrochloride, hydrobromide, maleate, sulphate or creatinine sulphate adduct) or a protected derivative such as an N-silyl derivative thereof with a reagent serving to introduce the group R_1SO_2.

Suitable reagents which serve to introduce the group R_1SO_2-include sulphonylating agents corresponding to the acid R_1SO_3H such as acid halides (for example sulphonyl chlorides) or acid anhydrides (for example sulphonic anhydrides).

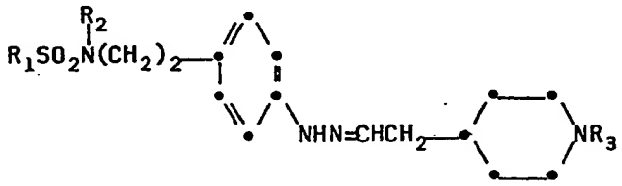
Compounds of formula (V) are novel and constitute a further feature of the invention.

The condensation process involving the sulphonylating agents may be effected in a suitable reaction medium which may be aqueous or non-aqueous and conveniently at a temperature of from -70 to +150°C. Thus the condensation reaction using an acid halide or anhydride may be effected in a suitable reaction medium such as an amide (e.g. N,N'-dimethylformamide), an ether (e.g. tetrahydrofuran), a nitrile (e.g. acetonitrile), a haloalkane (e.g. dichloromethane) or mixtures thereof, optionally in the presence of a base such as pyridine or triethylamine or an inorganic base as calcium carbonate or sodium bicarbonate. The organic base may also serve as a reaction solvent.

Compounds of formula (V) may be prepared by reduction of a corresponding compound having an appropriate reducible group as the 5-position substituent, such as $-CH_2CN$ using for example lithium aluminium hydride.

Such nitrile compounds are novel and constitute a further feature of the invention. These compounds may be prepared by any of the processes described hereinafter using starting materials in which the group $R_1SO_2NHCH_2$ is replaced by a nitrile group.

According to another general process (C), a compound of formula (I) may be prepared by cyclisation of a compound of formula (VI)



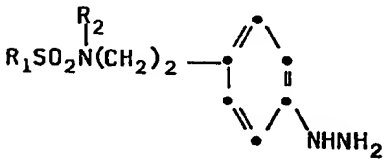
(VI)

The process is desirably carried out in the presence of polyphosphate ester in a reaction medium which may comprise one or more organic solvents, preferably halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, dichlorodifluoromethane, or mixtures thereof. Polyphosphate ester is a mixture of esters which may be prepared from phosphorus pentoxide, diethylether and chloroform according to the method described in 'Reagents for Organic Synthesis', (Fieser and Fieser, John Wiley and Sons 1967).

Alternatively the cyclisation may be carried out in aqueous or non-aqueous media, in the presence of an acid catalyst. When an aqueous medium is employed this may be an aqueous organic solvent such as an aqueous alcohol (e.g. methanol, ethanol or isopropanol) or an aqueous ether (e.g. dioxan or tetrahydrofuran) as well as mixtures of such solvents and the acid catalyst may be for example an inorganic acid such as concentrated hydrochloric, sulphuric or polyphosphoric acid. (In some cases the acid catalyst may also act as the reaction solvent). In an anhydrous reaction medium, which may comprise one or more alcohols or ethers (e.g. as described above) or esters (e.g. ethyl acetate), the acid catalyst will generally be a Lewis acid such as boron

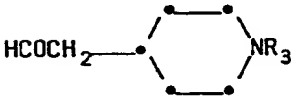
trifluoride, zinc chloride or magnesium chloride. The cyclisation reaction may conveniently be carried out at temperatures of from 20 to 200°C preferably 50 to 125°C.

According to a particular embodiment of this process, compounds of formula (I) may be prepared directly by the reaction of a compound of formula (VII):



(VII)

or a salt thereof, with a compound of formula (VIII)

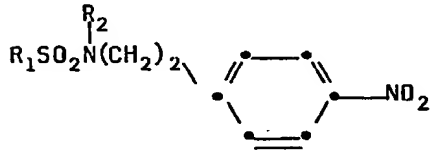


(VIII)

or a salt or protected derivative thereof (such as an acetal formed, for example, with an appropriate alkylorthoformate) using the appropriate conditions as described above. It will be appreciated that in this embodiment, a compound of formula (VI) is formed as an intermediate, and may be reacted in situ to form the desired compound of general formula (I).

Compounds of general formula (VI) may, if desired, be isolated as intermediates during the process for the preparation of compounds of formula (I) wherein a compound of formula (VII), or a salt or protected derivative thereof, is reacted with a compound of formula (VIII), or a salt or protected derivative thereof, in water or in a suitable solvent, such as an aqueous alcohol (e.g. methanol) at a temperature of, for example, 20 to 100°C. If an acetal or ketal of a compound of formula (VIII) is used, it is necessary to carry out the reaction in the presence of an acid (for example, acetic or hydrochloric acid).

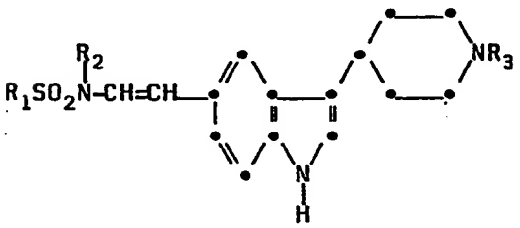
Compounds of general formula (VII) may be prepared in a number of conventional steps, from compounds of formula (IX):



(IX)

For example, a compound of formula (IX) may be reduced by catalytic hydrogenation using a catalyst such as palladium on charcoal to give an amine which may be diazotised using, for example nitrous acid and the product of this reaction may then be reduced using, for example, stannous chloride to give a compound of formula (VII).

According to another general process (D), a compound of formula (I) may be prepared by reduction of a compound of formula (X)

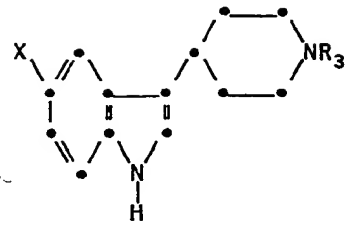


(X)

The reduction may be effected using similar reaction conditions to those described for general process (A) above.

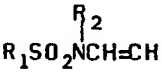
Compounds of formula (X) are novel and form a further feature of the invention.

Compounds of formula (X) may be prepared by reacting a compound of formula (XI)



(XI)

(wherein X represents a leaving atom or group such as a halogen atom for example a bromine atom) with an alkene



The reaction will generally be effected in the presence of a palladium catalyst and a base. The catalyst may be, for example, palladium on charcoal or a palladium salt. Palladium salts which may be employed as catalysts include salts of organic acids such as acetates or salts of inorganic acids such as chlorides or bromides. The base may be, for example, a tertiary nitrogen base such as triethylamine or tri-n-butylamine or an alkali metal carbonate such as sodium carbonate. The reaction may optionally be carried out in the presence of a phosphine, for example a triarylphosphine such as triphenylphosphine or tri-o-tolylphosphine. A phosphine should be present when the process is effected with a compound of formula (XI) wherein X represents a bromine atom.

General process (D) may be effected in the presence or absence of solvent. An anhydrous or aqueous reaction medium comprising one or more solvents may be employed. Suitable solvents include nitriles, for example, acetonitrile, alcohols, for example methanol, amides, for example dimethylformamide, N-methylpyrrolidone or hexamethylphosphoramide; and water. The reaction may conveniently be carried out at a temperature of from 25 to 200°C, preferably 75 to 150°C.

Compounds of formula (XI) may be prepared from known compounds by methods analogous to those described herein.

According to another general process (E) a compound of formula (I) according to the invention may be converted into another compound of the invention using conventional procedures.

According to one embodiment of general process (E), a compound of general formula (I) wherein one or more of R_2 and R_3 represent hydrogen atoms may be alkylated using conventional techniques. The reaction may be effected using a suitable alkylating agent such as an alkyl halide, alkyl tosylate or dialkylsulphate. The alkylation reaction may conveniently be carried out in an inert organic solvent such as an amide (e.g dimethylformamide) or an ether (e.g. tetrahydrofuran) preferably in the presence of a base. Suitable bases include, for example, alkali metal hydrides, such as sodium hydride, alkali metal carbonates, such as sodium carbonate or alkali metal alkoxides such as sodium or potassium methoxide, ethoxide or t-butoxide. The alkylation reaction is conveniently carried out at a temperature of from 25 to 100°C.

According to another general process (F), a compound of general formula (I) according to the invention, or a salt thereof may be prepared by subjecting a protected derivative of general formula (I) or a salt thereof to reaction to remove the protecting group or groups.

Thus, at an earlier stage in the preparation of a compound of general formula (I) or a salt thereof it may have been necessary and/or desirable to protect one or more sensitive groups in the molecule to prevent undesirable side reactions.

The protecting groups used in the preparation of compounds of formula (I) may be used in conventional manner. See for example 'Protective Groups in Organic Chemistry' Ed.J.F.W. McOmie (Plenum Press 1973) or 'Protective Groups in Organic Synthesis' by Theodora W Greene (John Wiley and Sons 1981).

In compounds of general formula (I) wherein R_3 represents hydrogen the group NR_3 may be protected for example by protonation or with a conventional amino protecting group. Such groups may include for example aralkyl groups, such as benzyl, diphenylmethyl or triphenylmethyl groups; and acyl groups such as N-benzyloxycarbonyl or t-butoxycarbonyl. The indole nitrogen may also be protected, for example by an aralkyl group such as benzyl or a trialkyl silyl derivative

Removal of any amino protecting groups present may be achieved by conventional procedures. Thus an aralkyl group such as benzyl, may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal); an acyl group such as N-benzyloxycarbonyl may be removed by hydrolysis with, for example, hydrogen bromide in acetic acid or by reduction, for example by catalytic hydrogenation.

As will be appreciated, in some of the general processes (A) to (E) described above it may be necessary or desired to protect any sensitive groups in the molecule as just described. Thus, a reaction step involving deprotection of a protected derivative of general formula (I) or a salt thereof may be carried out subsequent to any of the above described processes (A) to (E).

Thus, according to a further aspect of the invention, the following reactions may, if necessary and/or desired be carried out in any appropriate sequence subsequent to any of the processes (A) to (F).

(i) removal of any protecting groups; and

(ii) conversion of a compound of general formula (I) or a salt thereof into a pharmaceutically acceptable salt or solvate (for example, hydrate) thereof.

Where it is desired to isolate a compound of the invention as a salt, for example as an acid addition salt, this may be achieved by treating the free base of general formula (I) with an appropriate acid, preferably with an equivalent amount, or with creatinine sulphate in a suitable solvent (e.g. aqueous ethanol).

As well as being employed as the last main step in the preparative sequence, the general methods indicated above for the preparation of the compounds of the invention may also be used for the introduction of the desired groups at an intermediate stage in the preparation of the required compound. It should therefore be appreciated that in such multi-stage processes, the sequence of reactions should be chosen in order that the reaction conditions do not affect groups present in the molecule which are desired in the final product.

The invention is further illustrated by the following non-limiting Examples. All temperatures are in °C. Solvents were dried with Na_2SO_4 unless otherwise indicated.
Column chromatography was carried out either in the conventional manner using silica gel (Merck, Kieselgel 60, Art 7734) or by flash chromatography on silica (Merck 9385) except where otherwise stated.

Example 1

N-[2-[3-(1-Methyl-4-piperidinyl)-1H-indol-5-yl]ethyl]methanesulphonamide hydrochloride

(i) N-[2-(1H-Indol-5-yl)ethyl]methanesulphonamide

A mixture of 1-H-indole-5-ethanamine (0.29g), methanesulphonyl chloride (0.20ml), sodium bicarbonate solution (8%, 50ml) and ethyl acetate (50ml) was stirred at room temperature for 20min. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (50ml). The combined organic extract was washed with brine (50ml), dried ($MgSO_4$) and evaporated to dryness, giving an oil (0.43g) which was purified by chromatography eluting with ethyl acetate to give the title compound as an oil (0.35g). T.l.c. SiO_2, ethyl acetate Rf 0.58.

(ii) N-[2-[3-(1,2,3,6-Tetrahydro-1-methy-4-pyridinyl)-1H-indol-5-yl]ethyl]methanesulphonamide, potassium salt

A mixture of the product of Stage (i) (1.09g), 1-methyl-4-piperidone (1.0ml) and methanolic potassium hydroxide (2N; 25ml) was heated at reflux for 17h. The resulting solution was cooled to deposit the title compound as a solid (1.22g), m.p. 176-178°.

(iii) N-[2-[3-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethyl]methanesulphonamide hydrochloride

The product of Stage (ii) (0.93g) was dissolved in hydrochloric acid (2N, 15ml) and the resulting solution was basified in sodium carbonate solution (2N) and extracted with ethyl acetate. The insoluble solid (title compound free base, 0.28g) was filtered off and the combined organic extract was dried ($MgSO_4$) and evaporated to dryness to give more title compound base as a solid (0.42g) m.p. 198-200°. A sample of this material (0.21g) was dissolved in methanol (6ml) and treated with ethereal hydrogen chloride. On diluting with ether (30ml), the title salt was precipitated. This was triturated with ether (200ml) and then dried at 50° in vacuo to give the title compound as a solid (0.19g), m.p. 126-9°. (dec).

Analysis Found :	C,53.5;	H,6.2;	N,10.7;
$C_{17}H_{23}N_3O_2S.HCl.0.5H_2O$ requires :	C,53.9;	H,6.7;	N,11.1%

(iv) N-[2-[3-(1-Methyl-4-piperidinyl)-1H-indol-5-yl] ethyl]methanesulphonamide hydrochloride

A solution of the free base of the product of stage (iii) (0.33g) in ethanol (120ml) was hydrogenated at room temperature and pressure over pre-reduced 10% palladium on charcoal (50% aqueous paste; 0.38g) until hydrogen uptake had ceased. The catalyst was filtered off, and the filtrate was evaporated in vacuo to give a solid (0.31g) which was suspended in methanol (8ml) and treated with ethereal hydrogen chloride. The resulting solution was diluted with ether (100ml), and the precipitated solid triturated with ether to give the title compound as a solid (0.30g), m.p. 173-6° (dec) [shrinks at 167°]

Analysis Found :	C,51.9;	H,7.1;	N,10.4;
$C_{17}H_{25}N_3O_2S.HCl.1.25H_2O$ requires :	C,51.8;	H,7.3;	N,10.7%

Example 2

(i) N-[2-(1H-Indol-5-yl)ethyl]methanesulphonamide

A mixture of 1H-indole-5-ethanamine (1.00g), methane sulphonylchloride (0.69mℓ), 8% sodium bicarbonate solution (100mℓ) and ethyl acetate (100mℓ) were stirred vigorously for 20min. The organic phase was separated and the aqueous phase extracted with ethyl acetate (50mℓ). The combined organic phases were dried and evaporated in vacuo to give the title compound as an oil (1.50g). T.l.c. SiO_2, EtOAC Rf 0.8

(ii) N-[2-[3-(1,2,3,6-Tetrahydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]ethyl]methanesulphonamide

A mixture of the product of stage (i) (1.49g), 1-methyl-4-piperidone (1.35mℓ) and potassium hydroxide (3.9g, 70.0mmol) in methanol (35mℓ) was heated at reflux for 27h. The mixture was allowed to cool and the title compound crystallised out as a solid which was filtered off and washed with cold methanol (5mℓ). (1.00g) m.p. 170-172°.

(iii) N-[2-[3-(1-Methyl-4-piperidinyl)-1H-indol-5-yl] ethyl]methane sulphonamide

The product of stage (ii) (1.00g) in ethanolic hydrogen chloride (200mℓ) was hydrogenated for 1h over pre-reduced 10% palladium on carbon (50% paste with water, 1.00g).

The catalyst was filtered off, washed with ethanol (50mℓ) and the combined filtrates were evaporated in vacuo to give impure material as a solid. Purification by flash chromatography eluting with a mixture of CH_2Cl_2/EtOH/NH_4OH (100:8:1) gave the title compound as a solid (0.40g) m.p. 227-228°.

Analysis Found:	C,60.9;	H,7.6;	N,12.4.
$C_{17}H_{25}N_3O_2S$ requires	C,60.9;	H,7.5;	N,12.5%.

The following examples illustrate pharmaceutical formulations according to the invention containing N-[2-[3-(1-Methyl-4-piperidinyl)-1H-indol-5-yl]ethyl]methanesulphonamide as the active ingredient. Other compounds of the invention may be formulated in a similar manner.

A. Direct Compression

A. Direct Compression

1.	mg/tablet
Active ingredient	50
Magnesium Stearate BP	0.65
Anhydrous Lactose	80

The active ingredient is sieved and blended with the anhydrous lactose and magnesium stearate. The resultant mix is compressed into tablets using a Manesty F3 tablet machine fitted with 8.0mm concave punches.

2.	mg/tablet
Active ingredient	50
Magnesium Stearate BP	0.7
Microcrystalline Cellulose NF	90

The active ingredient is sieved and blended with the microcrystalline cellulose and magnesium stearate. The resultant mix is compressed into tablets using a Manesty F3 tablet machine fitted with 8.0mm concave punches.

B WET GRANULATION

	mg/tablet
Active ingredient	50.0
Lactose BP	153.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
Compression weight	250.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the

granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using suitable diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

The tablets may be film coated with suitable film-forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated, or enteric coated.

CAPSULES

	mg/capsule
Active Ingredient	50.00
*Starch 1500	149.00
Magnesium Stearate BP	1.00
Fill Weight	200.00

* A form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No.2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary changing the capsule size to suit.

SYRUP

Sucrose Free Presentation	mg/5ml dose
Active Ingredient	50.00
Hydroxypropylmethylcellulose USP (viscosity type 4000)	22.5
Buffer, Flavour, Colour, Preservative, Sweetener	as required
Purified Water BP to	5.0ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

SUSPENSION

	mg/5ml dose
Active ingredient	50.00
Aluminium monostearate	75.00
Sweetening agent, Flavour, Colour	as required
Fractionated coconut oil to	5.00ml

The aluminium monostearate is dispersed in about 90% of the fractionated coconut oil. The resulting suspension is heated to 115°C while stirring and then cooled. The sweetening agent, flavour and colour are

added and the active ingredient is suitably dispersed. The suspension is made up to volume with the remaining fractionated coconut oil and mixed.

SUB-LINGUAL TABLET

	mg/tablet
Active Ingredient	50.00
Compressible Sugar NF	49.5
Magnesium Stearate BP	0.5
Compression Weight	100.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of other strengths may be prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

SUPPOSITORY FOR RECTAL ADMINISTRATION

Active Ingredient	50.0mg
* Witepsol H15 to	1.0g

* A proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient in molten Witepsol is prepared and filled, using suitable machinery, into 1g size suppository moulds.

INJECTION FOR INTRAVENOUS ADMINISTRATION

	mg/ml
Sodium Chloride Intravenous Infusion, BP, 0.9% w/v	1.0 to 1 ml
Batch Size	2500ml

INJECTION FOR SUB-CUTANEOUS ADMINISTRATION

	mg/ml
Active Ingredient	20.0
Sodium Chloride BP, 0.9% w/w	to 1ml.

The active ingredient is dissolved in a portion of the Sodium Chloride Intravenous Infusion, the solution made to volume with the Sodium Chloride Intravenous Infusion, and the solution thoroughly mixed. The solution is filled into clear, Type 1, glass 10ml ampoules and sealed under a nitrogen headspace by fusion of the glass The ampoules are sterilised by autoclaving at 121°C for not less than 15 minutes.

FOR INHALATION

Inhalation Cartridges

	mg/cartridge
Active Ingredient (micronised)	1.00
Lactose BP	to 25.00

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler such as the Glaxo Rotahaler.

Metered Dose Pressurised Aerosol

Suspension Aerosol	mg/metered dose	Per can
Active ingredient (micronised)	0.500	132.00mg
Oleic Acid BP	0.050	13.2mg
Trichlorofluoromethane BP	23.12	5.55g
Dichlorodifluoromethane BP	61.25	14.70g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The oleic acid is mixed with the trichloromethane at a temperature of 10-15°C and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering 85mg of suspension are crimped onto the cans and the dichlorodifluoromethane is pressure filled into the cans through the valves.

Nasal Spray

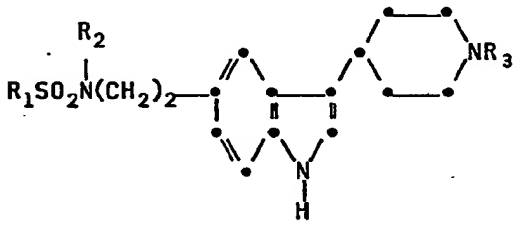
	% w/v
Active Ingredient	10.0
Preservative	as required
Sodium Chloride BP	
Purified Water BP to	100
Shot Weight	100mg (equivalent to 10mg active ingredient)

The active ingredient, preservative and sodium chloride are dissolved in a portion of the water, the solution made to volume with the water and the solution thoroughly mixed.

The pH may be adjusted, using acid or alkali, to that of optimum stability and/or to facilitate solution of the active ingredient. Alternatively, suitable buffer salts may be used.

Claims

1. A compound of formula (I)



(I)

wherein
R_1 represents a C_{1-6} alkyl group;
R_2 represents a hydrogen atom or a C_{1-6} alkyl group;
R_3 represents a hydrogen atom or a C_{1-3} alkyl group;
and pharmaceutically acceptable salts and solvates thereof.

2. A compound according Claim 1 wherein R_1 represents a C_{1-3} alkyl group.

3. A compound according to Claim 1 or 2 wherein R_2 represents a hydrogen atom.

4. A compound according to any of Claims 1 to 3 wherein R_3 represents a C_{1-3} alkyl group.

5. N-[2-[3-(1-Methyl-4-piperidinyl-1H-indol-5-yl]ethyl]methanesulphonamide and pharmaceutically acceptable salts and solvates thereof.

6. A compound according to any of Claims 1 to 5 for use in therapy.

7. The use of a compound according to any of Claims 1 to 5 in the preparation of a medicament for use in the treatment of conditions associated with cephalic pain.

8. The use of a compound according to any of Claims 1 to 5 in the preparation of a medicament for use

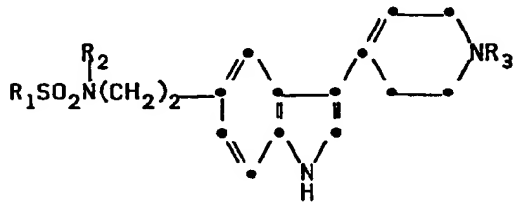
in the treatment of migraine cluster headache, chronic paroxysmal hemicrania or headache associated with vascular disorders and in alleviating the symptoms associated therewith.

9. A pharmaceutical composition which comprises at least one compound of formula (I) as defined in Claim 1 or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers or excipients.

10. A pharmaceutical composition as claimed in Claim 9 adapted for oral, parenteral or intranasal administration.

11. A pharmaceutical composition according to Claim 9 or 10 which is formulated in unit dosage form comprising 0.1mg to 100mg of active ingredient.

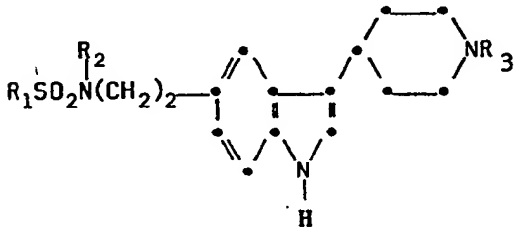
12. A compound of formula (II)



wherein R_1, R_2 and R_3 are as defined in Claim 1.

Claims for the following Contracting States: ES, GR

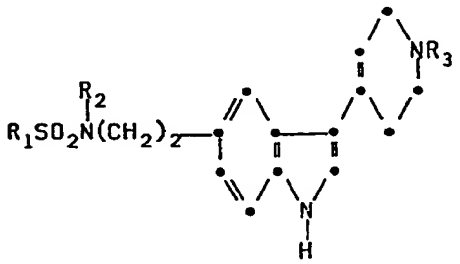
1. A process for the preparation of a compound of formula (I)



(I)

wherein
R_1 represents a C_{1-6} alkyl group;
R_2 represents a hydrogen atom or a C_{1-6} alkyl group;
R_3 represents a hydrogen atom or a C_{1-3} alkyl group;
and pharmaceutically acceptable salts and solvates thereof which comprises :

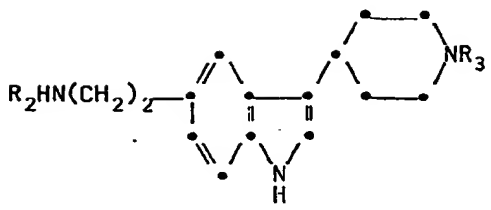
(A) reducing a compound of formula (II)



(II)

(wherein R_1, R_2 and R_3 are as defined for formula (I);
or

(B) condensing a compound of formula (V)

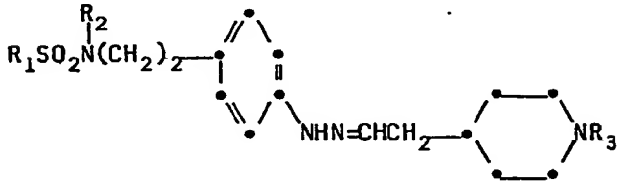


(V)

(wherein R_2 and R_3 are as defined for formula (I)) with a sulphonylating agent corresponding to an acid R_1SO_3H (wherein R_1 is as defined in formula (I)).

or

(C) cyclising a compound of formula (VI)

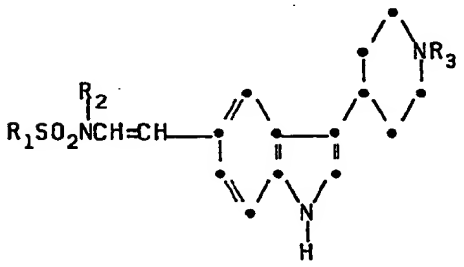


(VI)

(wherein R_1, R_2 and R_3 are as defined for formula (I));

or

(D) reducing a compound of formula (X)



(X)

(wherein R_1, R_2 and R_3 are as defined for formula (I));

or

(E) subjecting another compound of formula (I) to an interconversion reaction;

or

(F) subjecting a protected derivative of a compound of formula (I) or a salt thereof to reaction to remove the protecting group or groups; and if necessary or desired subjecting the compound resulting from any of steps (A) to (E) to one or two further reactions comprising :

i) removing any protecting groups

ii) converting a compound of formula (I) or a salt thereof into a pharmaceutically acceptable salt or solvate thereof.

2. A process according to Claim 1 wherein R_1 represents a C_{1-3} alkyl group.

3. A process according to Claim 1 or 2 wherein R_2 represents a hydrogen atom.

4. A process according to any of Claims 1 to 3 wherein R_3 represents a C_{1-3} alkyl group.

5. A process according to Claim 1 wherein the product is N-[2-[3-(1-methyl-4-piperidinyl-1H-indol-5-yl]ethyl]methanesulphonamide or a pharmaceutically acceptable salt or solvate thereof.

6. A process according to any of Claims 1 to 5 wherein in step (A) or (D) the reaction is effected in the presence of hydrogen and a catalyst at a temperature of from $^{-}10$ to $^{+}50°C$.

7. A process according to any of Claims 1 to 5 wherein in step (B) the reaction is effected using an acylating agent corresponding to an acid R_1SO_3H at a temperature of from $^{-}70$ to $^{+}150°C$, optionally in the presence of a base.

8. A process according to any of Claims 1 to 5 wherein in step (C) the reaction is effected at a temperature of from 20 to 200°C.

9. A process according to any of Claims 1 to 5 wherein in step (E) a compound of formula (I) wherein one or more of R_2 and R_3 are alkyl groups is prepared by alkylating a corresponding compound of formula (I) wherein one or more of R_2 and R_3 represent hydrogen atoms.

10. A process for preparing a pharmaceutical composition comprising admixing a compound of formula

(I) as defined in Claim 1 or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers or excipients.